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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/469,485 | 12/22/1999 | QINJIAN ZHAO | 20369Y | 5022 |

210 7590 11/05/2003

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EXAMINER

FOLEY, SHANON A

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1648

DATE MAILED: 11/05/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/469,485

Applicant(s)

ZHAO ET AL.

Examiner

Shanon Foley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. (US 4,620,948) and Valenzuela et al. (Nature. 1979; 280: 815-819) for reasons of record.

It is noted that applicant compares and contrasts the teachings of Builder et al. and Wampler et al. Applicant states that Wampler et al. demonstrates that the method of using oxidized and reduced glutathione to refold proteins did not work. Applicant argues that the reference is relevant and that the examiner is unresponsive to applicant's remarks for not addressing the teachings of Wampler et al.

However, on page 3, lines 4-6 of the Office action mailed May 5, 20003, the Office clearly explains why the teachings of Wampler et al. are not relevant to the instant claims. Wampler et al. do not teach the claimed method of purifying HBsAg. Wampler et al. do not teach the temperature or the length of time of incubation required by the claims. How can a completely different method, that did not work, provide motivation or a reasonable expectation of success for the instant method? This appears to be the point the applicant is making and the examiner agrees, which is why the teachings of Wampler et al. are not considered relevant. The rejection of record concerns the combined teachings of Builder et al. and Valenzuela et al. **and no other** (emphasis added).

With respect to the teachings of Builder et al., applicant reiterates the description of Builder's invention for refolding insoluble proteins produced in refractile bodies. Applicant points out that Builder et al. includes the steps of centrifuging the cell lysate and discarding the supernatant, which would contain soluble HBsAg antigens. Applicant also argues that Valenzuala et al. only provides motivation to achieve proper folding of HBsAg, but does not remedy the deficiencies of Builder et al. Applicant argues that Builder et al. is not relevant because the reference teaches dissolving insoluble proteins.

Applicant's arguments have been fully considered, but are found unpersuasive. Although the Builder et al. teach dissolving insoluble proteins, the reference emphasizes reactivation of proteins with a method to ensure proper folding. Builder et al. emphasize the importance of correct disulfide bond formation to obtain a biologically active protein, which is obtained by adding 10mM GSH: 1mM GSSG and incubating the mixture overnight at 37°C, see column 3, lines 34-68, examples 13 and 14 and column 16, lines 29-55. The strong denaturing solution completely denatures proteins in the refractile bodies while not interfering with the biological activity or stability. After the proteins are solubilized, Builder et al. teach adding 10mM GSH: 1mM GSSG to the solubilized protein and incubating the mixture overnight at 37°C to permit the proper refolding into correct disulfide bond formation. This is the same treatment method required for the instantly soluble HBsAg. Builder et al. clearly demonstrate a more than reasonable expectation of success for achieving a properly folded protein with steps claimed by the instant method. The only limitation missing from Builder et al. is the purification of HBsAg. However, Valenzuala et al. clearly provides a motivation for obtaining a correctly folded HBsAg antigen, which is even admitted by applicant. Therefore, a prima facie case of obviousness has

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been established. The combined teachings of Builder et al. and Valenzuela et al. teach all of the limitations in the claims, provide a motivation for the ordinary artisan to combine the references and produce the invention with a more than reasonable expectation of success.

Claims 17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. and Valenzuela et al. as applied to claims 8-16 above, and further in view of Petre et al. (WO 93/24148 A1) for reasons of record.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. and Valenzuela et al. as applied to claims 8-16 and 20 above, and further in view of Even-Chen (US 5,242,812) for reasons of record.

Applicant argues that the teachings of Petre et al. or Even-Chen do not remedy the deficiency of Builder et al. and Valenzuela et al. However, it is maintained that there is no deficiency in the teachings of Builder et al. and Valenzuela et al. for reasons discussed above. Therefore, it is maintained that claims 17, 19, 20, and 18 are prima facie obvious in view of the teachings of Builder et al. and Valenzuela et al. in further view of Petre et al. and Even-Chen, respectively.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Shanon Foley


JAMES HOUSEL 11/3/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600